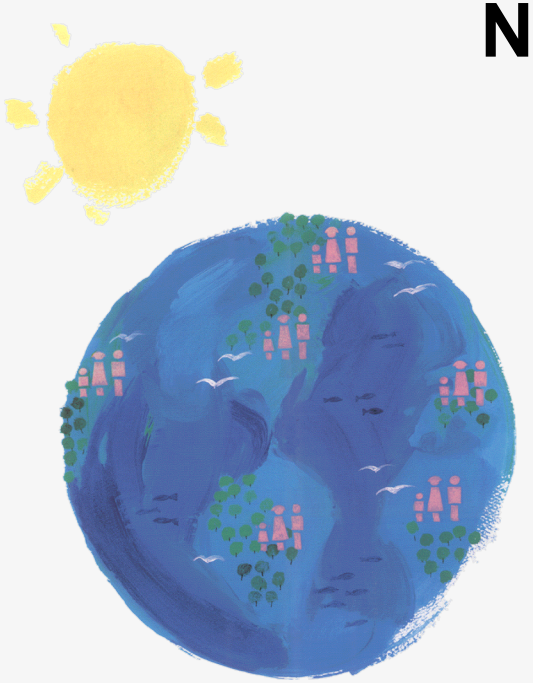
# NICEATM

*National Toxicology Program*
*Interagency Center for the Evaluation of Alternative Toxicological Methods*

# ICCVAM

*Interagency Coordinating Committee on the Validation of Alternative Methods*



# NICEATM-ICCVAM 5-Year Plan:
## Overview of Draft Plan

**Marilyn Wind, PhD.**

**Chair, ICCVAM**

7th Meeting of the Scientific Advisory Committee on Alternative Toxicological Methods

June 12, 2007
Marriott Bethesda North Hotel and Conference Center
Bethesda, MD

National Toxicology Program

NIEHS

National Institutes of Health

Department of Health & Human Services • USA

This presentation reflects the views of the author, has not been reviewed or approved by, and may not necessarily reflect the view of the U.S. Consumer Product Safety Commission.

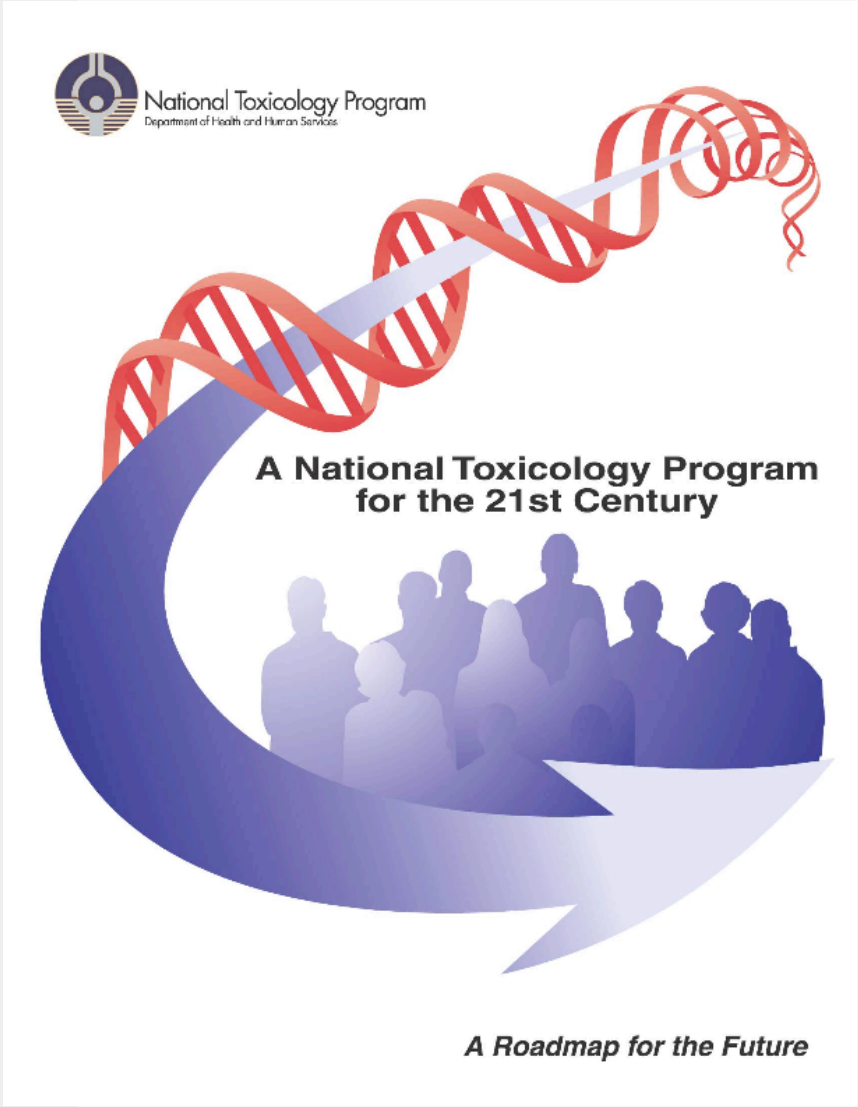
# NICEATM-ICCVAM 5-Year Plan

# Background

# U.S. House and Senate Appropriations Committees, Fiscal Year 2007 Requests

- **Requests NICEATM/ICCVAM, in partnership with relevant Federal agency program offices, to build on the NTP Roadmap to create five-year plan to:**
  - **Research,**
  - **Develop,**
  - **Translate, and**
  - **Validate** new and revised non-animal and other alternative assays for integration of relevant and reliable methods into the Federal agency testing programs.
- **Expects Federal agency program offices to:**
  - Identify areas of high priority for new and revised non-animal and alternative assays or batteries of those assays to create a path forward for the 3R's, when this is scientifically valid and appropriate.
- **Plan Requested by:**
  - **Senate: Status, Spring 2007**
  - **House: November 15, 2007**

# Building on NTP Roadmap




- Goal 2 of the Roadmap:
  - "Develop and validate improved testing methods and, where feasible, ensure that they reduce, refine, or replace the use of animals."

- From page 7:
  - *"Activities and assays developed under the NTP Roadmap will be done in cooperation and consultation with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) to maximize their value to regulatory agencies."*

# NIEHS Guidance to NICEATM and ICCVAM

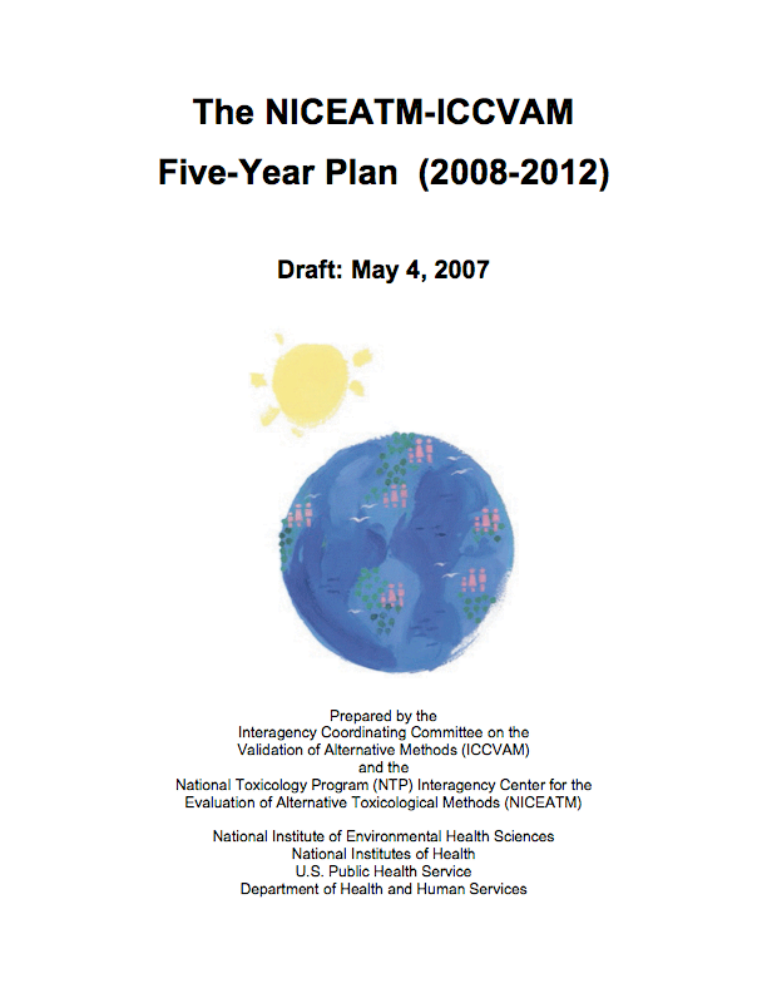
## - for development of Congressional Appropriations Committee Report (5-Year Plan)

- Report should be aimed at an audience of policymakers (Congress Members and staff)
- Body of report should be limited to no more than 20 pages
- Report must be submitted to NIEHS Budget Office by September 15, 2007 in order to complete clearance by congressional deadline of November 15, 2007

# Summary

- **NICEATM and ICCVAM, in partnership with relevant federal agency program offices, are preparing a congressionally-mandated five-year plan to**
  1. **Research, Develop, Translate, and Validate** new and revised non-animal and other alternative assays for integration of relevant and reliable methods into the Federal agency testing programs
  2. **Identify areas of high priority for new and revised non-animal and alternative assays** or batteries of those assays to create a path forward for the 3Rs, when this is scientifically valid and appropriate
- **Today we are presenting a draft of this Plan for your comment**
- **SACATM and public comments will be considered in finalizing the Plan**
- **The final Plan will be submitted to the congressional budget committees by November 15, 2007**
- **It will be made available to the public after submission to congress**

# Draft NICEATM-ICCVAM Five-Year Plan[1]



**The NICEATM-ICCVAM**

**Five-Year Plan (2008-2012)**

**Draft: May 4, 2007**

Prepared by the
Interagency Coordinating Committee on the
Validation of Alternative Methods (ICCVAM)
and the
National Toxicology Program (NTP) Interagency Center for the
Evaluation of Alternative Toxicological Methods (NICEATM)

National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Public Health Service
Department of Health and Human Services

- *Federal Register* Notice published May 1, 2007 (Vol. 72, No. 83, pp. 23832-23833)
  - Announce availability of the draft Plan
  - Request public comments on the draft Plan

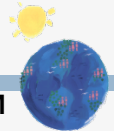
[1]Available at http://iccvam.niehs.nih.gov/docs/5yearplan.htm

# Plan Overview

- Introduction
- Chapters 1-4: 4 Key Challenges
  1. Identify priority areas and conduct and facilitate activities in these areas
  2. Identify research initiatives that are expected to support the future development of innovative alternative test methods
  3. Foster acceptance and appropriate use of alternative test methods through outreach and communication
  4. Develop partnerships and strengthen interactions with stakeholders in order to facilitate meaningful progress
- References and Information Resources
- Glossary of Terms
- Acronyms and Abbreviations
- Appendices







# 5-Year Plan: Introduction

- Agencies have mandates to protect human and animal health and the environment (See Appendix A)
  - In order to fulfill these mandates agencies must ensure that substances are safe, or properly labeled if hazardous
  - Current test methods and strategies involve the use of laboratory animals, *in vitro* methods, and/or *in silico* methods

- Agencies must determine if alternative test methods can provide equal or better protection of human and animal health and the environment before their adoption or endorsement
  - The ICCVAM Authorization Act of 2000 requires that new, revised, and alternative test methods must be determined to be valid before agencies can adopt them for regulatory purposes (See Appendix E)

[1]ICCVAM Authorization Act of 2000, 42 U.S.C. 285l–3

# 5-Year Plan Introduction: Current U.S. Laws

- U.S. laws (42 USC 289d, 7 USC 2131 et. seq.) require, prior to the use of animals for research and testing, that alternatives be considered and used where appropriate that will[1]:
  - Reduce the number of animals to the minimum required to obtain scientifically valid data
  - Refine procedures to lessen or eliminate pain and distress to animals
  - Replace animals with non-animal systems or with a phylogenetically lower animal species

[1]all of ICCVAM's activities are grounded in the *U.S. Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training*
http://grants.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples

# 5-Year Plan Introduction: Roles of ICCVAM and NICEATM

- NICEATM and ICCVAM work with stakeholders to facilitate research,development, translation, and validation activities
  - Depend on stakeholders to conduct and achieve successful test method research, development, translation, and validation
  - ICCVAM reviews submissions from stakeholders to determine the validation status and usefulness and limitations of new and revised test methods
- Federal agencies with statutory authority to conduct research, development, translation, and/or validation activities:
  - Department of Defense
  - Department of Energy
  - Environmental Protection Agency
  - Department of the Interior
  - NIEHS/NTP
  - Food and Drug Administration
  - NIOSH
  - ATSDR
  - NIH
  - National Cancer Institute
  - Department of Agriculture

# Key Challenges for NICEATM-ICCVAM

1. **Identify priority areas and conduct and facilitate activities in these areas**
2. Identify research initiatives that are expected to support the future development of innovative alternative test methods
3. Foster acceptance and appropriate use of alternative test methods through outreach and communication
4. Develop partnerships and strengthen interactions with stakeholders in order to facilitate meaningful progress

# Challenge 1: Identify priority areas and conduct and facilitate activities in these areas

- Addressed in Chapter 1
  - ***Current and Planned Activities for Priority Test Methods to Reduce, Refine, and Replace Animals in Regulatory Testing***
- ICCVAM test method prioritization criteria
  1. Potential impact on reducing, refining, or replacing animals for testing
  2. Potential to improve prediction of adverse health or environmental effects
  3. Applicability to multiple agencies
- Priorities may vary across Agencies
- Priorities may change
  - Need to be flexible so we can take advantage of advances in science and technology and availability of new methods

# Chapter 1: Current priority areas[1]

- Ocular Toxicity Testing
- Acute Toxicity Testing
- Biologics/Vaccines Testing
- Dermal Toxicity Testing
- Immunotoxicity Testing
- Endocrine Disruptor Testing
- Pyrogen Testing
- Chronic Toxicity/Carcinogenicity Testing

[1]These priorities are likely to evolve in response to new testing needs and advances

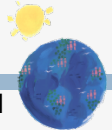
# Ocular Toxicity Testing

- High Priority
  - Multiple regulatory agencies require that ocular hazards be identified to warn consumers and workers
  - Potential for significant pain and distress to test animals

- Planned activities include:
  - Improve non-animal methods to detect permanent eye damage
  - Assess non-animal methods to detect reversible eye damage
  - Collect reference data to facilitate validation studies
  - Evaluate new methods or combinations/batteries of *in vitro* methods
  - Review routine use of topical anesthetics and systemic analgesics for reducing pain and distress







# Acute Systemic Toxicity Testing
## (oral, dermal, inhalation)

- High priority
  - Most common toxicity test conducted worldwide
  - Testing required by several federal agencies
  - Potential for significant pain and distress to test animals

- Planned activities include:
  - Review non-animal methods to reduce animal use for mixtures (a significant percentage of studies)
  - Expand reference database to facilitate the development and validation of other new *in vitro* tests (or batteries of tests)
  - Organize an international workshop to identify earlier, more humane endpoints and predictive batteries of *in vitro* test methods
  - Foster use of *in vitro* methods by the regulated community

# Biologics/Vaccines Testing

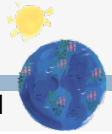
- High priority
  - Testing typically requires large numbers of animals
  - Potential for significant pain and distress to test animals
- Planned activities include
  - Follow and foster the development of alternative methods for vaccine potency testing
    - A priority will be an *in vitro* potency test being developed by the USDA
  - Review candidate alternative methods
  - Facilitate the acceptance of humane endpoints

# Dermal Toxicity Testing

- High Priority
  - Multiple agencies require that dermal hazards be identified to warn consumers and workers
  - Potential to cause significant pain and distress to test animals

- Planned activities include
  - Evaluate a combination (or battery) of *in vitro* test methods for evaluating skin corrosivity and irritation
  - Evaluate *in vitro* approaches for determining the skin irritation potential of antimicrobial cleaning products





# Immunotoxicity Testing: Allergic Contact Dermatitis

- High Priority
  - Multiple agencies require that the skin sensitizing hazards be identified to warn consumers and workers
  - Traditional test has potential to cause significant pain and distress; partially replaced by LLNA
- Planned activities include
  - Evaluate ability of LLNA to determine potency
  - Evaluate modifications to the LLNA
    - non-radiolabeled methods
    - a limit dose approach
  - Expand the scope and usefulness of the LLNA (eliminates pain and distress)

# Endocrine Disruptor Testing

- High Priority
  - Congress mandated that EPA develop and implement a screening and testing program for endocrine disruptors
  - Potential for large numbers of animals; castration/ovariectomy required for screening tests

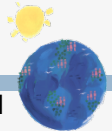
- Planned activities include
  - Complete an international validation study to evaluate an *in vitro* method to identify estrogen-like compounds
    - Eliminate the need for tissue donor animals
  - Increase involvement in OECD test guideline activities related to estrogen disruptors.
    - Promote standardized and adequately validated test methods

# Pyrogen Testing

- High Priority
  - Injectable or implanted drugs and devices must be shown to be free of substances that could cause fever
  - Current testing requires animals if existing *in vitro* method (BET) cannot be used

- Planned activities include
  - Develop final recommendations for five *in vitro* pyrogen tests
    - current usefulness and limitations
    - standardized protocols and future studies
    - performance standards
  - Encourage additional studies needed to expand applicability
  - Revisit validation status once additional studies are completed





# Chronic Toxicity/Carcinogenicity Testing

- High Priority
  - Current *in vivo* methods use large numbers of animals and two years to conduct
  - Cancer and chronic disease may cause significant pain and distress to test animals

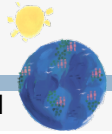
- Planned activities include
  - Participate in a JaCVAM-sponsored international validation of the the alkaline Comet assay to evaluate DNA damage in cells
    - If the JaCVAM validation study is successful, participate in validation of an *in vitro* Comet assay for use in a battery of genotoxicity tests.

# Other Toxicity Areas of Interest

- Neurotoxicity testing
- Reproductive and developmental toxicity testing
- Planned activities include
  - Monitor ongoing research activities
  - Identify the most useful tests
  - Facilitate their development and validation
  - Formally evaluate validation status for regulatory testing







# Key Challenges for NICEATM-ICCVAM

1. Identify priority areas and conduct and facilitate activities in these areas
2. **Identify research initiatives that are expected to support the future development of innovative alternative test methods**
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# Challenge 2: Identify research that may lead to future innovative alternative test methods

- Addressed in Chapter 2 – *Advances in Science and Technology*
- Several agencies have research and development programs
  - ICCVAM will monitor these for potential use in regulatory testing
- Areas currently identified as potentially applicable
  - High Throughput Screening
  - Other Animal Systems (Lower Species)
  - Computational Approaches
  - Biomarkers of Toxicity
  - Nanomaterials Testing Strategies
  - Toxicology Databases
- Most of these areas will require several years of development
- ICCVAM and NICEATM will continuously monitor federal agency and other stakeholders' research activities for additional areas of interest

# Challenge 2: Identify research that may lead to future innovative alternative test methods (continued)

- High Throughput Screening (HTS)
  - Conducive to the development of predictive *in vitro* test batteries
  - Potential to rapidly produce huge quantities of *in vitro* data
  - 1536 data points per plate versus 96 data points currently
  - Allows for different cell systems to be used at multiple concentrations
- Other Animal Systems
  - Phylogenetically lower animal systems offer quicker, less expensive tests
    - Genetic similarities and differences to humans are well understood
- Computational Approaches
  - Used in conjunction with HTS allows for rapid evaluation of large data sets
  - Can test large numbers of chemicals to determine priorities for further testing
  - May be used to assist in setting starting doses for further testing

# Challenge 2: Identify research that may lead to future innovative alternative test methods (continued)

- Biomarkers of Toxicity
  - May be used to predict damage to specific organs
  - May allow the use of more humane endpoints
  - May relieve pain and distress resulting from developing tumors and chronic disease
  - May assist with the development of *in vitro* screening tests
- Nanomaterials Testing
  - Nanomaterials are used across many technologies
  - Effect on toxicity of materials is largely unknown
  - Current tests may not be applicable or appropriate
- Toxicology Databases
  - Will provide high-quality animal test data
  - Will assist in the development of non-animal tests

# Key Challenges for NICEATM-ICCVAM

1. Identify priority areas and conduct and facilitate activities in these areas
2. Identify research initiatives that are expected to support the future development of innovative alternative test methods
3. **Foster acceptance and appropriate use of alternative test methods through outreach and communication**
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# Challenge 3: Foster Acceptance and Appropriate use of Alternative Test Methods

- Addressed in Chapter 3
  - *Fostering Acceptance and Appropriate use of Alternative Test Methods*
- Why is this important?
  - New and revised methods must be both accepted and used to impact the 3Rs
- How will ICCVAM foster acceptance and use of alternative test methods?
  - Provide guidance on adequate validation study design
  - Carry out high-quality public independent peer reviews
  - Provide comprehensive test method evaluations to regulatory agencies
  - Arrange implementation workshops

# Key Challenges for NICEATM-ICCVAM

1. Identify priority areas and conduct and facilitate activities in these areas
2. Identify research initiatives that are expected to support the future development of innovative alternative test methods
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4. **Develop partnerships and strengthen interactions with stakeholders in order to facilitate meaningful progress**

# Challenge 4: Develop partnerships and strengthen interactions with stakeholders

- Addressed in Chapter 4 – *Developing Partnerships and Strengthening Interactions with ICCVAM Stakeholders*
- Effective interactions are needed to stimulate alternative test method research, development, translation, and validation by stakeholders
- Partnerships will:
  - Best utilize existing resources
  - Maximize efficiency/minimize duplication of evaluation efforts
  - Ensure an early exchange of information
  - Facilitate national and international recognition, acceptance, and implementation of scientifically valid test methods

# Challenge 4: Develop partnerships and strengthen interactions with stakeholders (continued)

- How will we strengthen our interactions?
  - Strengthen international interactions with organizations such as OECD to foster appropriate development and validation of test methods
  - Foster interagency collaborations including validation studies
  - Collaborate with stakeholders to organize workshops to review state-of-the-art science and prioritize research, development, translation, and validation needed to advance the 3R's
  - Foster international collaborations by including experts from the international community on panels and workshops
  - Collaborate with ECVAM and JaCVAM to carry out independent validation studies

# What Do We Hope To Achieve?

- Further reduction and replacement of animal use where scientifically feasible
- Further reduction or elimination of pain and distress where animals are still used
- Continued protection of public health, animal health, and the environment

Thank you for your participation as we develop this Plan!

# Acknowledgements: ICCVAM Agency Representatives

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  - Dr. Amy Rispin
  - Dr. Margaret Snyder
  - Dr. William Stokes
  - Dr. Marilyn Wind, ICCVAM Chair
- **Agency Program Offices**
- **Stakeholders**